REDUCTION OF HETEROAROMATIC *N*-OXIDES WITH CARBON DISULFIDE AND ITS REGIOSELECTIVITY

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Abstract: Naphtho[2,1-*b*][1,5]naphthyridine 7,11-dioxide was prepared and deoxygenation of the *N*-oxide groups with carbon disulfide(CS_2) was reported. Of the two *N*-oxide groups, the 11-oxide was reduced with a 32% yield, whereas the 7-oxide remained unreacted. Molecular orbital calculations were then applied to rationalize the regioselectivity of CS_2 reduction of the known heteroaromatic *N*-oxides. The calculation result revealed that the electrophilic attack of CS_2 on the oxygen atom initiates the reaction. Subsequently, the reaction proceeds via a cyclic intermediate. When more than one intermediate is possible, the reaction through the more stable intermediate is preferred.

Introduction

Various polycyclic and heteroaromatic compounds exhibit mutagenicity and carcinogenicity. For example, benz[a]anthracene(1) and benzo[a]pyrene(2) derivatives are biologically oxidized or reduced and exhibit carcinogenicity, both in vitro and in vivo. On the other hand, some acridine derivatives are known as antileukemic agents(3). We oxidized and reduced naphtho[2,1-*b*][1,5]naphthyridine (7,11-diazabenzo[a]anthracene) **1** in connection with the biological interest.

Catalytic hydrogenation has been extensively used for the deoxygenation of heteroaromatic *N*-oxides. Otherwise, trivalent phosphorous compounds are useful reductants with superior selectivity(4). Furthermore, it is known that CS_2 is also a mild reductant of the *N*-oxide group. The selectivity of CS_2 is higher than the trivalent phosphorous compounds and it can react only on a positionally limited oxygen atom(5-7).

We also have an interest in this selectivity of CS_2 and synthesized naphtho[2,1-*b*][1,5]naphthyridine 7,11-dioxide **2** having two *N*-oxide groups in the molecule. We then heated the compound **2** with CS_2 in DMF-CH_2Cl_2 mixed solvent and exclusively obtained the 11-deoxy compound **3**. Furthermore, we tried to explain the reaction selectivity using molecular orbital calculations and confirmed that the reaction is initiated by the electrophilic attack of CS_2 on the *N*-oxide group, since the electron density of the oxygen atom has a relation to the reactivity. The reaction must then proceed via a cyclic intermediate as proposed by Seidl(5).

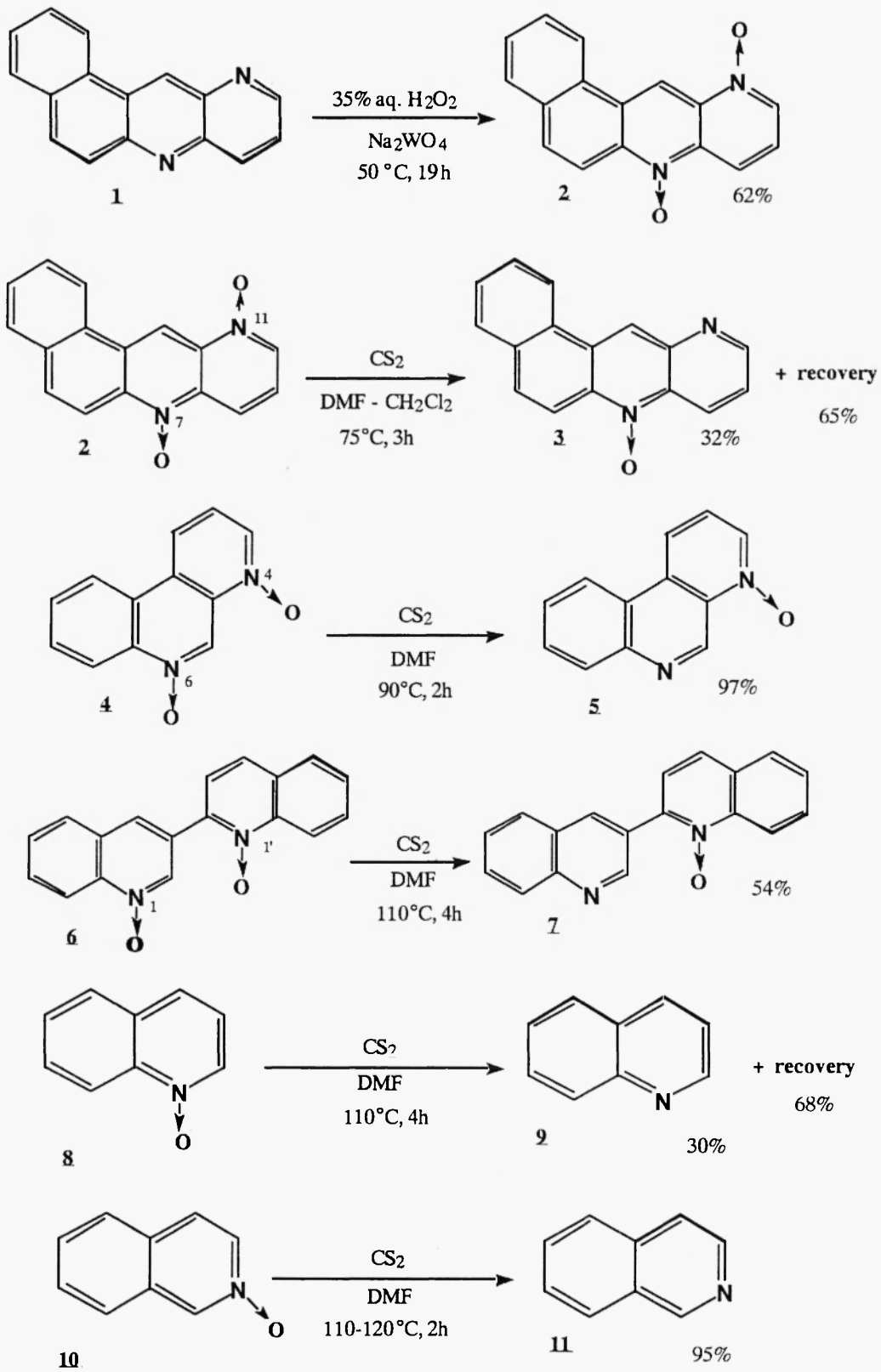
Experimental

Melting points were taken using a Yanagimoto micro-melting point hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a JEOL JMN GX-270 spectrometer at 270 MHz with tetramethylsilane (TMS) as the internal standard. Chemical shifts are given on the δ scale (ppm). The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, m=multiplet. Mass spectra (MS) were taken with a Hitachi GC-MS M-80 spectrometer. Infrared (IR) spectra were recorded using a JASCO IRA-I spectrometer.

Naphtho[2,1-*b*][1,5]naphthyridine 7,11-dioxide 2 A solution containing naphtho[2,1-*b*][1,5]naphthydine **1** (8)(0.20g, 0.87mmol), $Na_2WO_4 \cdot 2H_2O$ (0.06g), and 35% aq. H_2O_2 (2ml) was stirred and heated at 50-55°C for 19h. After the reaction was completed, the resulting precipitate was collected by filtration and washed with H_2O. The filtrate was dried and evaporated to afford solid product which was recrystallized from AcOEt to give 0.14g (62%) of **2** as yellow needles, mp 249-251°C. IR (KBr) ν_{max}(cm^{-1}): 1270 (N-O). MS *m/z*: 262 (M^+), 246 (M^+-O), 230 (M^+-2O). *Anal.* Calcd. for $C_{16}H_{10}N_2O_2$: C 73.27; H 3.84; N, 10.68. Found: C, 73.44; H, 3.60; N, 10.51. ^{1}H-NMR ($CDCl_3$) δ: 7.44-8.07(3H, m, 2-4H), 7.54(1H, dd, J=8.6, 6.6Hz, 9-H), 8.05 (1H, d, J=10.0Hz, 5-H), 8.63 (1H, d, J=10.0 Hz, 6-H), 8.66 (1H, dd, J=8.6, 1.6 Hz, 8-H), 8.74 (1H, m, 1-H), 8.85 (1H, dd, J=6.6, 1.6 Hz, 10-H), 9.68 (1H, s, 12-H).

Naphtho[2,1-*b*][1,5]naphthyridine 7-oxide 3 A mixture of **2** (66mg, 0.25mmol), *N,N*-dimethylformamide (DMF, 10ml), CH_2Cl_2 (20ml), and CS_2 (29mg, 0.38mmol) was heated at 75°C for 3h. The reaction mixture was poured into H_2O (30ml) and extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$. The solvent was evaporated to give a residue which was chromatographed over silica gel ($CHCl_3$) to give 20mg (32%) of **3** as yellow needles, mp 190-193°C (from AcOEt), and 40mg (65%) of the starting material **2** was recovered. IR (KBr) ν_{max}(cm^{-1}): 1250, 1270 (N-O). MS *m/z*: 246 (M^+), 230 (M^+-O). *Anal.* Calcd. for $C_{16}H_{10}N_2O$: C 78.03; H 4.09; N, 11.38. Found: C, 77.97; H, 3.83; N, 11.23. ^{1}H-NMR ($CDCl_3$) δ: 7.44-8.07(3H, m, 2-4H), 7.62(1H, dd, J=9.4, 4.0Hz, 9-H), 8.02 (1H, d, J=10.0Hz, 5-H), 8.74 (1H, d, J=10.0 Hz, 6-H), 8.74 (1H, dd, J=9.4, 1.6 Hz, 8-H), 9.13 (1h, dd, J=4.0, 1.6 Hz, 10-H), 9.20 (1H, s, 12-H), 9.22 (1H, m, 1-H).

Calculation Method Molecular orbital calculations were carried out using the PM3 method in the software package MOPAC Ver. 6.01 (9). The starting geometry was generated on a graphic display using the AVS/Chemistry Viewer (10) and all intramolecular flexibility was optimized by MOPAC. Mulliken population analysis was also done within MOPAC. All calculations were performed on a TITAN Vistra 800a workstation.

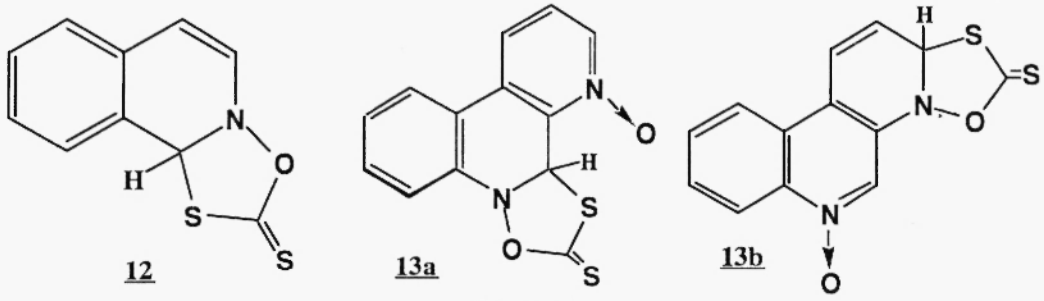

35% aq. H2O2
Na2WO4
50 °C, 19h
62%
CS2
DMF - CH2Cl2
75°C, 3h
+ recovery
65%
32%
CS2
DMF
90°C, 2h
97%
CS2
DMF
110°C, 4h
54%
CS2
DMF
110°C, 4h
+ recovery
68%
30%
CS2
DMF
110-120°C, 2h
95%

Scheme 1

Results and Discussion

Naphtho[2,1-*b*][1,5]naphthyridine 7,11-dioxide **2** was obtained from the corresponding heteroaromatic compound **1** (8). The deoxygenation of the dioxide **2** with CS_2 afforded the 7-oxy (11-deoxy) compound **3** in 32% yield. Recovery of the starting material was 65% and no 7-deoxy or 7,11-dideoxy compound was detected (Scheme 1). Thus, the reduction of the *N*-oxide groups of **2** by CS_2 was highly selective, especially CS_2 could not remove the 7-oxy group (11).

Previously, we also reported that 4,6-phenanthroline 4,6-dioxide **4** was reduced by CS_2 to give 4-oxide **5** in 97% yield. In this case, the oxygen atom located on the 4-*N* did not react with CS_2 (7). Noda et al. obtained 1′-oxide **7** in 54% yield from 3,2′-diquinolyl 1,1′-dioxide **6** and they did not detect any 1′-deoxy compounds (6). They also found that the CS_2 reduction of 1-quinoline 1-oxide **8** afforded 30% deoxy compound and 68% unchanged compound (6). Seidl et al. obtained 2-quinoline **11** from the *N*-oxide **10** in 95% yield by CS_2 reduction and they assumed that the reaction might proceed via an intermediate **12** (Scheme 2).



Scheme 2

As shown above, the CS_2 deoxygenation of the heteroaromatic *N*-oxide is so selective that it can reduce only a locationally limited oxygen. Namely, an *N*-oxide group, which has no hydrogen atom on the adjacent carbons, can not be reduced by CS_2 hence Seidl's intermediate is inconceivable. However, though compound **4** has two *N*-oxide groups, both of which can form intermediates as depicted by **13a** and **13b**, only one of them was reduced.

We then tried to explain these various reactivities using semiempirical molecular orbital calculations utilizing the PM3 method in the program package MOPAC (9). Since the CS_2 attack on the oxygen atom is considered to initiate the reaction (5), the electron density of the oxygen atoms was calculated. Table 1 shows the charge density of the oxygen atom calculated by applying Mulliken's population analysis. It can be seen that the more negative oxygen (negative than -0.62) suffers from the CS_2 attack, though the charge density was not proportional to the yield.

4,6-Phenanthroline 4,6-dioxide **4** has two *N*-oxide groups, both of which are possible to form the intermediates (**13a** and **b**). The heat of formation calculated using the PM3 method was 129.439 and 131.970 kcal/mol for **13a** and **13b**, respectively. The heat of formation of **13a** is 2.531 kcal lower than **13b**. Obviously, the reaction route whose intermediate is stabler, is chosen.

Finally, it may be concluded that an *N*-oxide, which is easy to accept the electrophilic attack of CS_2, is preferred in the first step, then the *N*-oxide, which can not possibly form the Seidl type intermediate, does not further react. Additionally, in case when two Seidl type intermediates are possible, the route including the more stable intermediate is selected.

Table 1: The reactivity of *N*-oxide and calculated charge density on the oxygen atom

Compound	Position of *N*-oxide	Yield (%)	Charge density of Oxygen
2	7	---	-0.606
	11	32	-0.628
4[a]	4	---	-0.613
	6	97	-0.624
6[b]	1	54	-0.627
	1′	---	-0.606
8[b]	1	30	-0.626
10[c]	2	95	-0.627

[a] Reference 7; [b] Reference 6; [c] Reference 5

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